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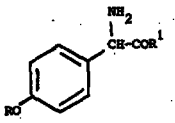
(19)

(54) PHARMACEUTICAL COMPOSITIONS

(71) We, PFIZER LIMITED, a British Company of Ramsgate Road, Sandwich, Kent, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to certain L- or DL (racemic)-phenylglycines, and to their use in treating diseases and conditions which are characterised by reduced blood flow, oxygen availability or carbohydrate metabolism in the cardiovascular system, such as ischaemic heart disease (particularly angina pectoris and myocardial infarction), cardiac failure, and cerebral insufficiency, or other diseases involving defects in carbohydrate metabolism, such as obesity and diabetes.

According to the invention there is provided a pharmaceutical composition comprising the L- or DL- (racemic) form of a compound of the formula:



— (I)

wherein R is H or CH_3 and R^1 is NH_2, OH or completes a carboxylic ester group, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier, said composition being in unit dosage form (as hereinafter defined).

When R^1 completes a carboxylic ester group, it is preferably a group of the formula —OR^2 wherein R^2 is a C_1—C_5 alkyl group, a phenyl group optionally substituted by C_1—C_4 alkyl, C_1—C_4 alkoxy or halogen, or an aryl-substituted C_1—C_4 alkyl group, said aryl group being a phenyl group optionally substituted by C_1—C_4 alkyl, C_1—C_4 alkoxy or halogen. In this specification, the term "halogen" indicates chlorine, bromine or iodine.

Pharmaceutically acceptable salts of compounds of the formula (I) may be addition salts with acids containing pharmaceutically acceptable anions, e.g. the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, p-toluene suphonate and carbonate salts. Pharmaceutically acceptable salts of compounds of the formula (I) in which R^1 is OH may also be salts containing pharmaceutically acceptable cations, e.g. the sodium, potassium, calcium and ammonium salts, and salts with amines or amino-acids, e.g. the salts with arginine, meglumine, ethanolaminine or choline.

The preferred phenyl glycine of the formula (I) i L(+)-2-(4-hydroxyphenyl)-glycine. D(−)-2-(4-hydroxyphenyl)glycine is substantially ineffective and the L(+) form of the compound is, therefore, signficantly more effective than the DL- (racemic) form at the same dose level.

By the term "unit dosage form" as used herein is meant a physically discrete unit containing an individual quantity of the active component in association with a pharmaceutically acceptable diluent or carrier, the quantity of active component being such that at least one unit or severable fraction of a unit is required for a single therapeutical administration. In the case of severable units, such as scored tablets, at least one severable fraction such as a ½ or ¼ of the unit may be all that is required for a single therapeutic administration. It will be appreciated that the term "unit

dosage form" does not include mere solutions except when the solutions are packaged in ingestible containers, e.g. soft capsules, or have been prepared so as to be suitable for parenteral administration, e.g. in vials of solution suitable for parenteral injection.

The compounds of the formula (I) are known compounds. Methods for the preparation of the DL- compounds and their subsequent resolution into the D- and L- forms are well known (see for Example British Patent Specification No. 1,423,822). However, no medical or any other use has previously been proposed for the L- forms of the compounds, or any medical use for the DL- (racemic) forms.

The compounds of the formula (I) may be administered to patients in admixture with or dissolved in a pharmaceutically acceptable carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, they may be administered orally in the form of tablets or capsules containing a unit dose of the compound of the formula (I) together with such excipients as maize starch, calcium carbonate, dicalcium phosphate, alginic acid, lactose, magnesium stearate, "Primojel" (Trade Mark) or talc. The tablets are typically prepared by granulating the ingredients together and compressing the resulting mixture to tablets of the desired size. The capsules are typically prepared by granulating the ingredients together and filling them into hard gelatine capsules of the appropriate size to contain the ingredients.

The compounds may also be administered parenterally, for example by intramuscular, intravenous or subcutaneous injection. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes, for example enough salts (e.g. sodium acetate, sodium lactate, sodium succinate or sodium chloride) or dextrose (e.g. 5% w/v anhydrous dextrose injection BP) to make the solution isotonic with blood. A pharmaceutically-acceptable organic solvent such as polyethylene glycol or ethanol may also replace part of the water. An antioxidant such as sodium metabisulphite may also be present, typically in an amount of up to 0.1% by weight.

Such parenteral formulations may be prepared by conventional methods. For example, in a typical procedure involving the preparation of a succinate-containing intravenous formulation, a 0.2 molar solution of succinic acid may be mixed with a 0.2 molar solution of sodium hydroxide to give a solution of pH5. The compound of the formula (I) is then typically dissolved in the succinate solution in an amount of 1—2% on a weight/volume basis. The resulting solution may then be sterilised according to the method of B.P. 1973 by filtration through a bacteria-proof filter under aseptic conditions into sterile containers so as to comply with the test for sterility of Appendix 121, B.P. 1973.

Alternatively, stable parenteral formulations based on isotonic saline solution may be prepared by successively dissolving an antioxidant, e.g. sodium metabisulphite, and sodium chloride in nitrogen-sparged water to give an approximately 0.1 molar sodium chloride solution, dissolving the compound of formula (I) in solution in an amount of 1—2% on a weight/volume basis and adjusting the pH to about 4 with 0.1N hydrochloric acid. The solution is then sterilised and filled into containers as already described.

Suitable containers are for example sterile glass vials of an appropriate size to contain the desired volume of solution, which volume will typically contain one or more unit doses of the compound of the formula (I). The compounds of the formula (I) may also be administered by the infusion of a parenteral formulation as described above into a vein.

For oral or parenteral administration to human patients, it is expected that the dosage level of the L- form of a compound of the formula (I) will be from 0.5 to 10, more probably 2—5, mg/kg for a typical adult patient (50—70 kg), up to 5 times a day. Thus tablets or capsules can generally be expected to contain from 25 mg to 500 mg of the active compound, one or more of which would be taken orally up to 5 times a day. Dosage units for parenteral administration can be expected to contain from 25—700 mg. of the active compound in 5—20 ml of solution. A typical vial could thus be a 50 ml vial containing from 5 to 35 mg of the active compound per ml in 30—50 ml of solution. The expected dosage level of the DL- (racemic) form of the compounds will of course be higher than that of the L- form.

It should of course be appreciated that the physician in any event will determine the actual dosage which will be most suitable for the individual and it will vary with the age, weight and response of the patient. The above dosages are exemplary of the average host.

There may of course be individual cases where higher or lower dosage ranges are merited.

The potential utility of the compounds of the formula (I) for treating disease or conditions characterised by reduced blood flow, oxygen availability or carbohydrate metabolism in the cardiovascular system, or other disease or condition involving a defect in carbohydrate metabolism, is assessed by their ability:

(1) to increase the oxidation of glucose and/or pyruvate by isolated rat muscle preparations *in vitro;*

(2) to increase the proportion of the active form of the enzyme pyruvate dehydrogenase (PDH) in organs of animals *in vivo*;

(3) to reduce oxygen demand and affect the relative utilisation of carbohydrate and lipid metabolites by the electrically-paced heart of anaesthetised dogs in the presence or absence of an isoprenaline stimulus; and

(4) to decrease blood glucose levels in animals made diabetic by chemical lesion of the pancreas.

Activity in tests for (1) is indicative of the potential utility of the compounds in the treatment of ischaemic heart disease, cardiac failure, cerebral insufficiency, maturity-onset diabetes or obesity.

Activity in tests for (2) is further indicative of their potential utility in the treatment of these diseases or conditions and, in particular, activity in an animal heart *in vivo* is indicative of utility in the treatment of ischaemic heart disease and cardiac failure.

Activity in tests for (3) is further indicative of their potential utility in the treatment of ischaemic heart disease and cardiac failure. Activity in tests for (4) is further indicative of their potential utility in the treatment of diabetes.

The preparation of unit dosage forms according to the invention is illustrated by the following Examples:—

EXAMPLE 1.

Glacial acetic acid (12.0 gm) and sodium acetate anhydrous (16.4 gm) were each dissolved in 1000 ml of freshly distilled water to produce 0.2 molar solutions. 148.0 ml of the acetic acid solution was then mixed with 352.0 ml of the sodium acetate solution and the mixture made up to 1000 ml with freshly distilled water. L(+)-2-(4-hydroxyphenyl)glycine (10.0 gm, 0.056 mole) was then added and the resulting 1% w/v solution of L(+)-2-(4-hydroxyphenyl)glycine had a pH of 5. This was then sterilised according to the method of the BP 1973 by filtration through a suitable bacteria-proof filter under aseptic conditions into sterile containers so as to comply with the test for sterility of Appendix 121, BP 1973. Suitable containers are sterile 50 ml glass vials, which when filled with 30 ml of the final solution, contain 300 mg of the active ingredient.

EXAMPLE 2.

Succinic acid (23.62 gm) and sodium hydroxide (8 g) were each dissolved in 1000 ml of freshly distilled water to produce 0.2 molar solutions. 250 ml of the succinic acid solution was then mixed with 267.0 ml of the sodium hydroxide and the mixture made up to 1000 ml with freshly distilled water. L(+)-2-(4-hydroxyphenyl)-glycine (10.0 gm, 0.056 mole) was then added and the resulting 1% w/v solution of L(+)-2-(4-hydroxyphenyl)glycine had a pH of 5. This was then sterilised as in Example 1. Sterile 50 ml glass vials, when fiilled with 40 ml of the final solution, contain 400 mg of the active ingredient.

EXAMPLE 3.

Citric acid monohydrate (21.0 gm) was dissolved in 200,0 ml of an 0.1 molar solution of sodium hydroxide in freshly distilled water and the resulting solution was made up to 1000 ml with freshly distilled and cooled water. 963.0 ml of this solution was then made up to 1000 ml with an 0.1 molar solution of hydrochloric acid in water. L(+) - 2 - (4 - hydroxyphenyl)glycine (10.0 gm, 0.056 mole) was then added to give a 1% w/v solution having a final pH of 5 at 23° C, which was then sterilised as in Example 1. Sterile 50 ml glass vials, when filled with 50 ml of the final solution, contain 500 mg of the active ingredient.

EXAMPLE 4.

750 ml of freshly distilled water were sparged with nitrogen and then 6.0 g sodium chloride, 300 mg of sodium metabisulphite (B.P.) and15 g of L(+) - 2 - (4 - hydroxyphenyl)glycine were added successively and stirred to dissolve. The pH was then adjusted to about 4.0 with 0.1N hydrochloric acid, the solution made up to 1 litre with freshly distilled water and the solution readjusted to pH 4.0±0.35 with 0.1N HCl, to give a stable, 1½% w/v isotonic saline solution of the active compound. This was sterilised as in Example 1 and filled into sterile 50 ml glass vials, which when filled with 50 ml of solution each contained 750 mg of the active ingredient. A nitrogen blanket was maintained over the solution throughout and the vials were purged with nitrogen before and after filling.

EXAMPLE 5.

Each of the above Examples 1 to 4 is repeated using twice the amount of DL (racemic) - 2 - (4 - hydroxyphenyl)glycine as that of the L(+) - isomer to give solutions containing twice the concentration of active ingredient.

EXAMPLE 6.

The following are typical tablet or capsule formulations containing L - (+)- 2 - (4 - hydroxyphenyl)glycine as active ingredient:

	mg/tablet or capsule				
	A	B	C	D	E
Active ingredient	500	100	100	25	25
Lactose	30	170	–	220	–
Maize starch	60	80	–	105	–
Microcrystalline cellulose ("Avicel")	–	–	170	–	220
Glycine	–	–	80	–	105
Fine silica ("Aerosil")	–	0.35	0.35	0.35	0.35
Magnesium stearate*	5	3	3	3	3
	595	.....	353.35	.....	.....

* 9:1 blend with sodium lauryl sulphate
"Avicel" and "Aerosil" are Trade Marks.

For formulations A, B and D, the ingredients are thoroughly blended together, and then either filled directly into hard gelatin capsules of appropriate size, or granulated and compressed into tablets of the desired size. For formulations C and E, the ingredients are thoroughly blended together and slugged.

The slugs are broken down into granules, and then either filled into capsules of the appropriate size, or directly compressed into tablets of the desired size.

In formulations A, B and D, the lactose may be replaced by equal amounts of calcium carbonate or dicalcium phosphate.

EXAMPLE 7.

Example 6 is repeated using the same amount of DL (racemic) - 2 - (4 - hydroxyphenyl)glycine as that of the L(+)-isomer. Of course, twice as many capsules or tablets of this example may be required to be taken for a single therapeutic administration as are required of the tablets or capsules of Examples 6.

EXAMPLE 8.

Examples 1 to 4 and 6 are repeated using equimolar amounts of the following compounds in place of L(+) - 2 - (4 - hydroxyphenyl)glycine:

L(+) - 2 - (4 - methoxyphenyl)glycine
Methyl L(+) - 2 - (4 - hydroxyphenyl)glycinate
Isopropyl L(+) - 2 - (4 - hydroxyphenyl)glycinate
2 - Methoxybutyl L(+) - 2 - (4 - hydroxyphenyl)glycinate
L(+) - 2 - (4 - hydroxyphenyl)glycinamide

EXAMPLE 9.

Examples 5 and 7 are repeated using equimolar amounts of the DL (racemic) compounds of Example 8 in place of DL (racemic) - 2 - (4 - hydroxyphenyl)glycine.

It may be advantageous to coat tablets according to the invention with an enteric coating, i.e. a coating of a material such as cellulose acetate-phthalate or hydroxypropylmethyl cellulose phthalate which does not dissolve in the stomach but dissolves in the intestine, and to include in the tablet composition an effervescent material, e.g. sodium bicarbonate and an edible acid such as tartaric acid, in order to avoid de-activation of the active ingredient in the stomach and/or intestine and to enhance the concentration of the active ingredient in the blood.

It may also be desirable to coat tablets with a sugar coating to improve palatability.

Compounds of the formula (I) have been tested for their ability to increase the oxidation of glucose and/or pyruvate by the following tests:—

(1) (a) Diaphragm tissue is obtained from rats fed on a high fat diet similar to 'Diet B' described by Zaragoza and Felber (Horm. Metab. Res. 1970, *2*, 323). Pyruvate oxidation by such tissue is assessed by measurement of the rate of incorporation of carbon-14 from carben-14-labelled pyruvate into carbon dioxide *in vitro*, as described by Bringolf (Eur. J. Biochem. 1972, *26*, 360). The rate of pyruvate oxidation is depressed by 50—75% compared with that by diaphragm tissue from rats fed on a normal diet. When L(+) - 2 - (4 - hydroxyphenyl)glycine is added to the medium, it is found to stimulate pyruvate oxidation by diaphragm tissue from fat-fed rats in a dose dependant manner. The threshold concentration for such stimulation is about 0.25 millimolar and a maximum stimulation of 170% is achieved at concentrations of 4 millimolar and above. D(−) - 2 - (4 - hydroxyphenyl)glycine has no significant effect on pyruvate oxidation by diaphragm tissue from fat-fed rats at concentrations up to 4 mM, while the DL (racemic)-compound has an effect approximately half that of the L(+)-isomer.

The degree of stimulation by other compounds of formula (I) at a concentration of 0.5 mM is shown in the following Table:—

Compound	% Stimulation
L(+)-2-(4-methoxyphenyl)glycine	79%
Methyl L(+)-2-(4-hydroxyphenyl) glycinate	89%
Isopropyl L(+)-2-(4-hydroxyphenyl) glycinate	34%
3-Methylbutyl L(+)-2-(4-hydroxyphenyl)-glycinate	32%
L(+)-2-(4-hydroxyphenyl) glycinamide	51%

(1) (b) The rate of glucose oxidation by isolated hearts from starved rats is measured in a recirculating oxygenated perfusion system, by measuring the rate of incorporation of carbon-14 from carbon-14-labelled glucose into carbon dioxide using a method similar to those described by Morgan *et al* (J. Biol. Chem. 1961, *236*, 253) and by Randle *et al* (Biochem. J. 1964, *93*, 652). The perfusate contains glucose, palmitate, insulin and bovine serum albumen. The normal rate of glucose oxidation is found to be 1.27±.32 micromoles/hour (mean of 9 observations). When L(+) - 2 - (4-hydroxyphenyl)glycine is included in the perfusate at a concentration of 2 millimolar, the rate of oxidation is increased to 4.77±1.53 micromoles/hour (mean of 9 observations). D(−) - 2 - (4 - hydroxyphenyl)glycine has no significant effect on the rate of oxidation when included in the perfusate at the same concentration.

The ability of compounds of formula (I) to increase the proportion of the active form of the pyruvate dehydrogenase enzyme has been measured in the following test:
(2) Rats fed on a high fat diet as in test (1) (a), are treated either with placebo or

with the compound of formula (I), by sub-cutaneous or intravenous injection or by oral administration, and at various times after treatment the rat hearts are removed and homogenised, under conditions which minimise changes in the proportion of the pyruvate dehydrogenase enzyme which is present in the active form, as described by Whitehouse and Randle (Biochem. J. 1973, *134*, 651). The total amount of the enzyme present (PDHt) and the amount which is present in the active form (PDHa) are assessed by a method similar to that described by Taylor *et al* (J. Biol. Chem. 1973, *248*, 73). The fat-feeding process is found to depress the ratio PDHa/PDHt from a normal value of about 0.7 to a value in the range from 0.05 to 0.2. Treatment of fat-fed rats with L(+) - 2 - (4 - hydroxyphenyl)glycine, either parenterally or orally, increases this ratio in a dose-dependant manner, the threshold doses for this effect being 0.05 millimole/kg by intravenous injection and in the range 0.1 to 0.2 millimole/kg by subcutaneous injection or by oral administration. The ratio is increased to a value in the range 0.8—1.0 (i.e. above that for rats on normal diet) by doses of 0.6 millimole/kg and above.

D(−) - 2 - (4 - hydroxyphenyl)glycine has very little effect at dose levels up to 1.2 millimole/kg, while the DL (racemic) compound, although having some activity, has only half, or less than half, the effect of the L(+) - isomer at the same dose levels.

The increase in the PDHa/PDHt ratio effected by other compounds of formula (I) at a dose level of 0.6 milimoles/kg is shown in the following Table:

Compound	dosage route (1)	PDHa/PDHt ratio	
		placebo	compound
Methyl L(+)-2-(4-hydroxyphenyl) glycinate	s.c.	0.13	0.69
	p.o.	0.13	0.42
3-Methylbutyl L(+)-2-(4-hydroxyphenyl) glycinate	s.c.	0.05	0.51
L(+)-2-(4-hydroxyphenyl) glycinamide	s.c.	0.16	0.93
	p.o.	0.16	0.91

(1) s.c. = sub-cutaneous, p.o. = oral

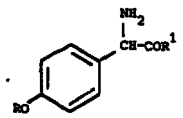
The ability of compounds of formula (I) to reduce oxygen demand and affect the relative utilisation of carbohydrate and lipid metabolites in the heart has been assessed by measuring the effect of the compounds on myocardial blood flow and metabolism is fasted, closed-chest, anaesthetised beagle dogs, with cardiac catheterisation to enable simultaneous sampling of coronary sinus and arterial blood to be carried out. Coronary sinus blood flow is measured by the hydrogen gas clearance technique described by Aukland *et al* (Circulation Res. 1964, *14*, 164). The heart is paced electrically at 155 beats/min. and recordings of haemodynamic parameters (blood pressure, left ventricular pressure and the first derivative of the latter) are made continuously. Control measurements of coronary blood flow are made and samples of blood taken at 40 min. intervals, both in an untreated animal and in the same animal dosed with an infusion of isoprenaline (60 ng/kg/min.), which both stimulates cardiac contraction and increases plasma free fatty acid levels. The compound of formula (I) is then administered intravenously and measurements are made and samples taken again, 40 minutes and 90 minutes later. The blood samples from the artery and coronary sinus are analysed for oxyhaemoglobin, pyruvate and free fatty acid (FFA) content, differences between those of the arterial and coronary sinus blood, when multiplied by coronary blood flow, being a measure of oxygen consumption, pyruvate uptake and FFA uptake by the myocardium respectively.

It is found that L(+) - 2 - (4 - hydroxyphenyl)glycine at doses of 0.02 to 0.1 millimole/kg increases myocardial pyruvate uptake by at least 2-fold, both in the presence and absence of isoprenaline, for a period of at least 90 minutes after dosing, in keeping with its proven action as a PDH stimulator. Myocardial blood flow is simultaneously increased by up to 150%, and myocardial oxygen consumption is decreased by about 20% in the presence of isoprenaline. Myocardial FFA uptake is affected to a variable extent, but is generally decreased. There is no affect on any of the haemodynamic parameters measured.

The ability of compounds of formula (I) to decrease blood glucose levels has been assessed by measuring their effect on blood glucose levels in rats in which diabetes has been induced by treatment with streptozotocin (85 mg/kg). Four days after such treatment, a number of rats are given 1 millimole/kg of the compound by intraperitoneal injection and a similar number are given placebo. The doses are repeated after a further 24 hours and 48 hours. Blood samples are taken from a tail vein immediately before each dosage (which is 2 hours after removal of the animals from food) and 1, 2, and 3 hours after the third dose. After 2 days of treatment with L(+) - 2 - (4-hydroxyphenyl)glycine (i.e. immediately before the third dose with 1 millimole/kg), blood glucose levels have been found to have declined from 378±8 mg/100 ml to 356±4 mg/100 ml, compared with a slight increase from 373±8 mg/100 ml to 383±10 mg/100 ml for animals treated with placebo; while 2 hours after the third dose the blood levels had declined still further, to a minimum value of 313±7 mg/100 ml, compared with a value of 385±7 mg/100 for animals treated with placebo (all figures are averages for 8 animals).

WHAT WE CLAIM IS:—

1. A pharmaceutical composition is unit dosage form comprising the L- or DL-(racemic) form of a compound of the formula:



— (I)

wherein R is H or CH_3 and R^1 is NH_2, OH or completes a carboxylic ester group, or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier.

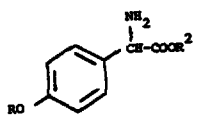
2. A composition as claimed in claim 1, in which the compound is L(+) - 2 - (4-hydroxyphenyl)glycine.

3. A composition as claimed in claim 1, in which the compound is DL-(racemic)-2 -(4 - hydroxyphenyl)glycine.

4. A composition as claimed in claim 1, in which the compound is L(+) - 2 - (4-methoxyphenyl)glycine.

5. A composition as claimed in claim 1, in which the compound is L(+) - 2-(4 - hydroxyphenyl)glycinamide.

6. A composition has claimed in claim 1, in which the compound has the formula:



in which R is H or CH_3 and R^2 is a C_{1-5} alkyl group, a phenyl group optionally substituted by a C_1—C_4 alkyl, C_1—C_4 alkoxy or halogen, or an aryl-substituted C_1—C_4 alkyl group, said aryl group being a phenyl group optionally substituted by C_1—C_4 alkyl, C_1—C_4 alkoxy or halogen.

7. A composition as claimed in claim 6, in which the compound is methyl L(+)-2 - (4 - hydroxyphenyl)glycinate, isopropyl L(+) - 2 - (4 - hydroxyphenyl)glycinate or 3 - methylbutyl L(+) - 2 - (4 - hydroxyphenyl)glycinate.

8. A composition as claimed in any of claims 1 to 7, in the form of a tablet or capsule containing from 25 mg to 500 mg of the compound.

9. A composition as claimed in any of claims 1 to 7, in the form of a solution prepared for parenteral administration containing from 5 to 35 mg of the compound per ml of solution.

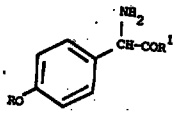
10. A vial containing one or more dosage units of a composition as claimed in claim 9.

11. A composition as claimed in claim 1, substantially as hereinbefore described with particular reference to any one of the Examples.

The ability of compounds of formula (I) to decrease blood glucose levels has been assessed by measuring their effect on blood glucose levels in rats in which diabetes has been induced by treatment with streptozotocin (85 mg/kg). Four days after such treatment, a number of rats are given 1 millimole/kg of the compound by intraperitoneal injection and a similar number are given placebo. The doses are repeated after a further 24 hours and 48 hours. Blood samples are taken from a tail vein immediately before each dosage (which is 2 hours after removal of the animals from food) and 1, 2, and 3 hours after the third dose. After 2 days of treatment with L(+) - 2 - (4-hydroxyphenyl)glycine (i.e. immediately before the third dose with 1 millimole/kg), blood glucose levels have been found to have declined from 378±8 mg/100 ml to 356±4 mg/100 ml, compared with a slight increase from 373±8 mg/100 ml to 383±10 mg/100 ml for animals treated with placebo; while 2 hours after the third dose the blood levels had declined still further, to a minimum value of 313±7 mg/100 ml, compared with a value of 385±7 mg/100 for animals treated with placebo (all figures are averages for 8 animals).

WHAT WE CLAIM IS:—

1. A pharmaceutical composition is unit dosage form comprising the L- or DL-(racemic) form of a compound of the formula:



— (I)

wherein R is H or CH_3 and R^1 is NH_2, OH or completes a carboxylic ester group, or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier.

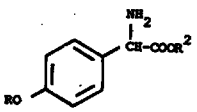
2. A composition as claimed in claim 1, in which the compound is L(+) - 2 - (4-hydroxyphenyl)glycine.

3. A composition as claimed in claim 1, in which the compound is DL-(racemic)-2 -(4 - hydroxyphenyl)glycine.

4. A composition as claimed in claim 1, in which the compound is L(+) - 2 - (4-methoxyphenyl)glycine.

5. A composition as claimed in claim 1, in which the compound is L(+) - 2-(4 - hydroxyphenyl)glycinamide.

6. A composition has claimed in claim 1, in which the compound has the formula:



in which R is H or CH_3 and R^2 is a C_{1-5} alkyl group, a phenyl group optionally substituted by a C_1—C_4 alkyl, C_1—C_4 alkoxy or halogen, or an aryl-substituted C_1—C_4 alkyl group, said aryl group being a phenyl group optionally substituted by C_1—C_4 alkyl, C_1—C_4 alkoxy or halogen.

7. A composition as claimed in claim 6, in which the compound is methyl L(+)-2 - (4 - hydroxyphenyl)glycinate, isopropyl L(+) - 2 - (4 - hydroxyphenyl)glycinate or 3 - methylbutyl L(+) - 2 - (4 - hydroxyphenyl)glycinate.

8. A composition as claimed in any of claims 1 to 7, in the form of a tablet or capsule containing from 25 mg to 500 mg of the compound.

9. A composition as claimed in any of claims 1 to 7, in the form of a solution prepared for parenteral administration containing from 5 to 35 mg of the compound per ml of solution.

10. A vial containing one or more dosage units of a composition as claimed in claim 9.

11. A composition as claimed in claim 1, substantially as hereinbefore described with particular reference to any one of the Examples.

(14)

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